IN THE SPECIFICATION

Please amend the specification as follows.

At page 5, insert after the heading "BRIEF DESCRIPTION OF THE DRAWINGS", at line 12:

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Amend the paragraph beginning on Page 6 at line 16, as follows:

Figure 7 (comprising Figures 7a and 7b) shows binding affinity assays of GST-GRIP1 constructs with NR-boxes 1, 2, and/or 3 and their interaction with TR [[LBD.]] LBD (Figure 7b). GRIP-1 NR boxes 1, 2 and 3 interact differently with TRβ LBD. Single letter designations are used for the amino ~~acids.~~ acids (Figure 7a).

Amend the paragraph beginning on Page 6 at line 19, as follows:

Figure 8 (comprising Figures 8a and 8b) shows binding affinity assays of GST-GRIP1 constructs with NR-boxes 1,2, and/or 3 and their interaction with TR and GR LBDs. TR and GR differ in their interactions with GRIP-1.

Amend the paragraph beginning on Page 6 at line 22, as follows:

Figure 9 (comprising Figures 9a and 9b) shows binding affinity assays for NR-box 2- and 3-peptides and GRIP1 and their interaction with TR LBD. NR box 2- and 3-containing peptides (Figure 9b) reproduce the affinity and specificity of the NR interaction ~~domain.~~ domain (Figure 9a).

Amend the paragraph beginning on Page 6 at line 25, as follows:

Figure 10 (comprising Figures 10a, 10b and 10c) shows binding affinity assays for NR-box 2- and 3-peptides and their interaction with TR LBD. ~~Sequence~~ Sequences adjacent to the (SEQ ID NO: 1) LxxLL motif modulate the affinity of NR-box-TRβ LBD interactions.

Amend the paragraph beginning on Page 6 at line 28, as follows:

Figure 11 (comprising Figures 11a, 11b and 11c) shows binding affinity assays for mutant GRIP1 and NR-box 2- and 3-peptides and their interaction with TR LBD. The individual leucine residues of the (SEQ ID NO: 1) LxxLL motif are crucial for binding of the GRIP-1 NR interaction domain to TRβ LBD.

Amend the paragraph beginning on Page 7 at line 30, as follows:

Figure 17 shows complementarity between the (SEQ ID NO: 1) LxxLL motif and the surface of the hTR LBD. The side chains of the (SEQ ID NO: 2) ILxxLL motif are shown in a CPK representation, with the main chain of the peptide drawn as a C-alpha trace. The three ~~leucinee~~ leucine residues fit into pockets of the coactivator binding site of the hTRβ LBD, depicted as mesh, while the isoleucine residue rests on the edge of the site's cleft.

Amend the paragraph beginning on Page 31 at line 21 (including the immediately following header), as follows:

Binding assays show that GRIP1 NR-boxes 1, 2 and 3, interact differentially with hTRβ LBD (Figure [[7).]] 7b). A GST-fusion of the GRIP1 (563-767) fragment strongly binds TR (kD or EC50) in a ligand [[depend]] dependent fashion. Replacement of the hydrophobic residues of NR-box 3 with alanine does not reduce binding of TR significantly, whereas similar replacement of NR-box 2 results in loss of TR binding of about 50%. By titrating the amount of GRIP1 fragment, about a 4-fold stronger binding of TR for NR-box 2 (EC50 = 1.0 μM) over NR-box 3 (EC50 = 4.0 μM) was estimated. In the absence of functional NR-boxes 2 and 3, almost no binding to TR was detected suggesting that under these experimental conditions NR-box 1 is not a cognate binding site for TR. Full length TR or TR-LBD bound GRIP1 equally. These results show that TR recognizes GRIP1 NR-box 2 and 3, with preference for NR-box 2.

Example 11: Coactivator NR-box binding affinity for GR

Amend the paragraph beginning on Page 31 at line 32 (including the immediately following header), as follows:

GR also was found to bind GRIP1 (563-767) in a ligand-dependent manner. ~~manner (Figure 8).~~ However, in contrast to TR, extension of GRIP1 (563-767) to residue 1121 increases binding to GR about 3-fold suggesting an additional binding site on GRIP1 for

[[GR.]] GR Figure 8a. Binding of the larger fragment remains ligand-dependent; no interaction can be observed in the presence of the GR partial antagonist RU486. These results are in agreement with *in vivo* 2-hybrid GR GRIP1 interaction studies. In the presence of ligand no difference was detected in the binding of GRIP1 by full length GR or a deletion mutant of GR that lacks the N-terminal activation domain AF-1. However in the absence of ligand, binding of GR to GRIP1 (563-1121) increased by about 10-fold indicating that sequences in the GR. N-terminus are able to suppress binding of unliganded GR to this additional binding site in GRIP1. Additionally, (Figure 8b) GR did not bind to a GRIP1 (563-767) mutant in which both *NR*-box 2 and 3 are replaced by alanines, and binds most strongly to a fragment that lacks a functional NR-box 2. As with TR, GR does not recognize NR-box 1. In contrast to TR, the GR prefers NR-box 3 to NR-box 2. These results demonstrate that GR prefers binding to NR-box 3 and interacts with an additional GRIP1 site within the CREB (cAMP - response - element binding protein) - binding protein (CBP) binding site.

Example 12: Coactivator peptide binding affinity for TR

Amend the paragraph beginning on Page 32 at line 17, as follows:

To investigate whether the preference of TR for NR-box 2 is dependent on the sequence or structural context of the NR-boxes, competition studies on the interaction of GRIP1 with hTRβ LBD were performed using coactivator peptides containing different NR-boxes (NR-box 2 peptide (residues 11-23 of SEQ ID NO: 6) EKHKILHRLLQDS, and NR-box 3 peptide (residues 9-21 of SEQ ID NO: 7) ENALLRYLLDKDD) (**Figure [[9**).]] 9b). Consistent with the interaction of hTRt LBDβ with GRIP1 (563-767) NR-box mutants, a peptide containing NR-box 1 competes with the interaction of GRIP1 with hTRβ LBD only at very high concentrations (EC50 = 130 μM). Peptides containing either NR-box 2 or 3 compete with GRIP1 (563-767) efficiently and display the preference of hTRβ LBD for NR-box 2 (EC50 (NR-box 2) = 1.5 μM, EC50 (NR-box 3) = 4 μM). The apparent affinities (EC50) for peptides of NR-box 2 and 3 are comparable with the analogous GRIP1 (563-767) NR-box mutants suggesting that the preference of it for NR-boxes is solely dependent on the sequence and independent of the structural context of the NR-boxes.

Amend the paragraph beginning on Page 32 at line 29, as follows:

Peptides of NR-box 2 or 3 compete with GRIP1 (563-767) containing functional NR-boxes 2 and 3 or a mutant of this fragment that contains only a functional NR-box 2 with comparable affinity. Thus, while TR can bind both NR-box 2 and 3, in a GRIP1 coactivator peptide fragment containing both boxes, TR preferentially binds NR-box 2.

Amend the paragraph beginning on Page 33 at line 9, as follows:

Sequence identity between all three central NR-boxes of the p160 coactivator family is limited to the conserved leucine residues of the (SEQ ID NO: 1) LxxLL motif (Figure 6). However, the sequence conservation of a particular NR-box can extend into neighboring residues. To investigate the contribution of these neighboring residues to affinity and specificity of the different NR-boxes for TR, the ability of peptides containing individual NR-boxes with different lengths of adjacent sequences to compete with the interaction of GRIP1 (563-767) with hTRβ LBD were compared ~~(Figure 10).~~ (Figures 10a, 10b, and 10c)

Amend the paragraph beginning on Page 33 at line 16, as follows:

A peptide (Figure 10b) consisting of the minimal motif of NR-box 3 (residues 12-17 of SEQ ID NO: 7; LLRYLL) does not compete with the TR LBD interaction with GRIP1 (563-767). A peptide consisting of the NR-box 2 (residues 15-20 of SEQ ID NO: 6; ILHRLL) also does not sufficiently compete with the interaction (data not shown). Extending peptides containing a (SEQ ID NO: 1) LxxLL motif to include adjacent residues increased affinity for both NR-box motifs and magnified the preference of TR for NR-box 2 (NR-box 2 ~~peptides:~~ peptides in Figure 10a: (residues 11-23 SEQ ID NO: 6) EKHKILHRLLQDS and (residues 7-23 of SEQ ID NO: 6) TSLKEKHKILHRLLQDS; and NR-box 3 ~~peptides:~~ peptides in Figure 10b: (residues 8-24 of SEQ ID NO: 7) KENALLRYLLDKDDTKD and (residues 5-24 of SEQ ID NO: 7) PKKKENALLRYLLDKDDTKD). A chimeric peptide containing the NR-box 3 motif in the context of the NR-box 2 flanking sequences (SEQ ID NO: [[31;]] 29; TSLKEKHKLLRYLLQDSS) binds like a NR-box 2 ~~peptide.~~ peptide (Figure 10c).

Amend the paragraph beginning on Page 33 at line 32, as follows:

To investigate the role of the hydrophobic residues in NR-box 2, individual residues of the (residues 15-20 of SEQ ID NO: 6) ILHRLL motif were replaced by alanine in the background of GRIP1 (563-767) containing a non-functional NR-box 3 (**Figure** [[**11**).]] 11a).

Surprisingly, replacement of any of the conserved leucines prevents binding to TR almost completely. Only replacement of the nonconserved isoleucine exhibited a lessened but still severe impact on the affinity of NR-box 2 for TR. As replacement of a single leucine by alanine is sufficient to overcome the interaction of both the remaining hydrophobic residues and adjacent sequences with hTRβ LBD, it appears that their contribution to the affinity of NR-box 2 for hTRβ LBD is cooperative rather than additive.

Amend the paragraph beginning on Page 34 at line 10, as follows:

Similar results were obtained by competing the interaction of hTRβ LBD with the GRIP1 (563-767) NR-box 3 mutant using peptides in which either IL, HR or LL of the NR-box 2 motif are replaced by alanines (**Figure** [[**11**).]] 11b). Whereas the peptides containing the IL or LL replacement failed to interact with the hTRβ LBD even at very high concentrations, in agreement with a proposed alpha-helical structure of the motif, replacement of the "HR spacer" by alanines showed a marginal effect on the affinity of the peptide for TR-LBD.

Amend the paragraph beginning on Page 34 at line 16, as follows:

Replacement of single leucine residues of NR-box 2 by phenylalanine reduced the affinity of NR-box 2 peptides for TR LBD about 100-fold, replacement of the isoleucine about 10-fold (Figure [[11).]] 11c). Therefore, the interaction of TR with GRIP1 relies not simply on the hydrophobicity of the (SEQ ID NO: 1) LxxLL motif, but also on positive contributions by the leucine residues themselves.